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Pilot study of anakinra to mitigate CAR-T toxicity in subjects with relapsed or refractory large B-cell lymphoma

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Investigational Drug: Anakinra

Source of Investigational Drug: Sobi

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1.0 TRIAL SUMMARY

Abbreviated Title	Pilot study of anakinra to mitigate CAR-T toxicity in relapsed or refractory large B-cell lymphoma
Clinical Indication	The treatment of adult subjects with relapsed or refractory large B-cell lymphoma who receive axicabtagene ciloleucel (axi-cel) CAR T-cell therapy
Trial Type	Interventional
Route of administration	Subcutaneous
Trial Blinding	Unblinded, open-label
Treatment Groups	Subjects will receive anakinra by subcutaneous injection for 7 days starting on day 0 of axi-cel treatment. Anakinra will be tested at a dose level of 100 mg daily and 100 mg BID. A 3+3 design will be used for a safety run-in phase within each dose level of Anakinra
Number of trial subjects	Maximum of 20 with 10 subjects per dose level cohort.
Estimated duration of trial	It is estimated that the trial will require approximately 12 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	This is a single institution, open-label pilot study. Each subject will participate in the trial from the time the subject signs the Informed Consent through the final protocol-specified time period. Subjects with r/r diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (tFL) after at least 2 systemic therapies and who are otherwise eligible to receive standard of care axi-cel therapy will be enrolled. Anakinra will be administered by subcutaneous injection daily for 7 days starting on day 0 of axi-cel treatment. The primary objective is to assess the safety and tolerability of anakinra when used as a prophylactic strategy to mitigate toxicity associated with use of CAR T cells. Secondary objectives include the incidence of different grades and duration of both CRS and ICANS, overall and complete response rates, progression-free survival (PFS), and overall survival (OS). Exploratory objectives include determining CAR T cell levels in the blood, serum cytokine and chemokine levels, and effect on the phenotype and/or function of monocytes.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single center, open label, pilot study of anakinra in combination with axi-cel in subjects with relapsed or refractory large B-cell lymphoma. A maximum of 20 subjects will be enrolled in this trial to examine the safety, tolerability and efficacy of anakinra administered subcutaneously at a dose of 100 mg daily (N=10) or 100 mg BID (N=10), starting on day 0 of axi-cel infusion, for 7 days. A 3+ 3 design will be used for a safety run-in phase within each dose level cohort. Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. ASTCT consensus guidelines will be applied to grade CRS and ICANS. Response will be determined according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.[1]

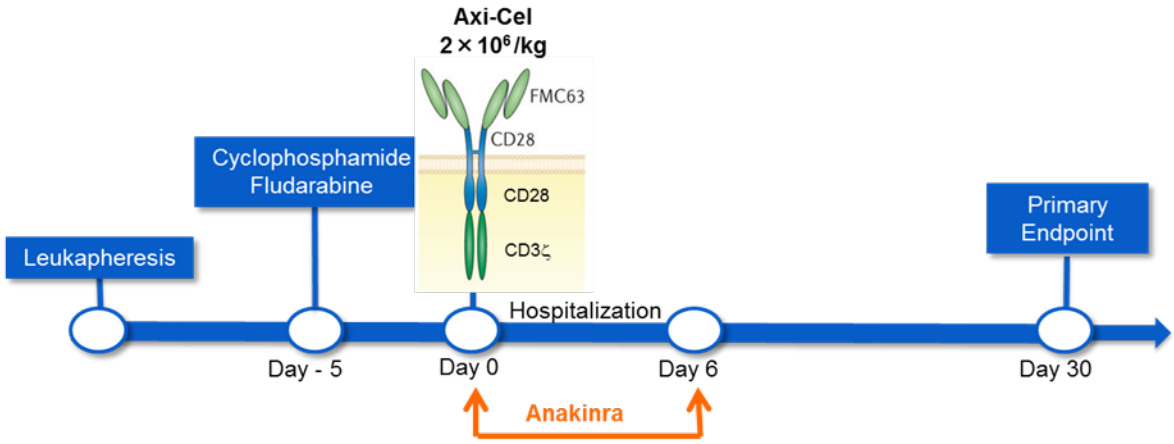
Patients will be followed until documented progression of disease (PD), unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has completed 2 years of follow-up. After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events (SAEs) will be collected for 30 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

The primary objective of the trial is to assess safety and tolerability of anakinra in reducing incidence of CRS within 30 days after infusion of CAR T cells. Secondary objectives include incidence of different grades and duration of both CRS and ICANS, overall response rate (ORR) complete response rate (CRR), progression-free survival (PFS), and overall survival (OS). Exploratory objectives include evaluation of pharmacodynamics effects of anakinra, and biomarkers of toxicity, response and resistance.
This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in **Figure 1**.



- CRS and ICANS assessment daily while hospitalized and at each clinic visit for first 30 days
- Tumor assessment at baseline and months 1, 3, 6, 9, 12, 18, 24
- Blood samples (PBMC and plasma) days -5, -1, 0, 1, 3, 5, 7, 9, 11, 13, 21, 28, 90, 180, 270, 360

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** The primary objective of the study is to assess safety and tolerability of anakinra in reducing incidence of CRS within 30 days after infusion of CAR T cells in subjects with relapsed or refractory large B-cell lymphoma.

Hypothesis: Anakinra will be safe, well-tolerated and effective in decreasing the incidence of axi-cel-related CRS in patients with r/r large B-cell lymphoma.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine incidence of all grades and duration of both CRS and ICANS.

(2) **Objective**: To determine the CRR, ORR, PFS and OS.

Hypothesis: Administration of anakinra in the setting of axi-cel therapy will decrease incidence of all grades and duration of both CRS and ICANS in patients with r/r large B-cell lymphoma. Response rates and survival with anakinra and axi-cel therapy will be comparable to those observed with axi-cel alone in patients with r/r large B-cell lymphoma.

3.3 Exploratory Objective

(1) **Objective:** To determine the effects of anakinra on the cytokine and chemokine profile in peripheral blood after CAR-T therapy.

(2) **Objective:** To determine the effects of anakinra on the expansion and persistence of CAR T cells.

(3) **Objective:** To correlate baseline characteristics with toxicity, response and survival after anakinra combined with CAR-T therapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma

Outcomes with first- and second-line therapies in large B-cell lymphoma. Approximately 60% of patients affected by aggressive B-cell lymphoma are cured with the use of frontline chemoimmunotherapy.[2-4] Salvage high-dose chemotherapy followed by autologous stem cell transplant is potentially curative after failure of frontline therapy.[5] However, only 50% of patients who relapse after frontline chemoimmunotherapy are transplant-eligible, because of age, performance status or comorbidities. Of these, only half will respond to salvage chemotherapy, and of those who will respond and will be able to proceed to transplant, less than half will be cured.[6,7] As a consequence, novel effective and safe therapies are desperately needed for patients with relapsed or refractory aggressive B-cell lymphoma.

CAR T cell biology. Chimeric antigen receptor (CAR) modified T cells are a form of adoptive cellular therapy, employing genetically engineered T lymphocytes, created in the laboratory in 1989, but refined and brought to the clinic only in the last few years.[8] Autologous T cells are collected from the patient usually through leukapheresis, engineered with CAR and expanded ex vivo, and subsequently reinfused (ideally after conditioning). Unlike donor T lymphocytes employed in allogeneic stem cell transplant or endogenous T cells that recognize unique antigens expressed on tumor cells through a HLA-restricted manner via their naturally expressed T-cell receptor, CAR T cells recognize antigens on tumor cells in an HLA-independent mechanism via their artificially expressed receptor. This allows broad therapeutic use of CAR T cells generated from either autologous or allogeneic source and also likely overcomes tumor escape mediated by low HLA expression.[9]

First generation CAR T cells. CARs are formed of 3 parts: an extracellular, a transmembrane and an intracellular domain. The extracellular domain is usually a single-chain variable fragment (scFv) derived from the variable heavy and light chains of an antibody targeting a specific tumor antigen (e.g. CD19 in B-cell lymphomas). Upon engagement with its cognate antigen, the extracellular domain initiates the activation signal to the CAR T cell via the intracellular domain.[10] The first generation of CAR T cells was composed of an extracellular domain recognizing a target tumor antigen, and an intracellular signaling domain, CD3ζ, which mediates signal 1 to the T-lymphocyte. However, limited efficacy was observed with this structure.[11]

Second generation CAR T cells. In the second generation CARs, the intracellular domain is typically composed of two signaling domains: CD3ζ to provide signal 1 and a co-stimulatory domain, which mediates signal 2 and promotes the proliferation, cytotoxic activity, and persistence of CAR T cells. The 2 most commonly used co-stimulatory domains are CD28 and CD137 (4-1BB).[12] Investigators at Baylor College of Medicine treated 6 patients affected by relapsed refractory B-cell lymphoma (including DLBCL, t-FL and chronic lymphocytic leukemia [CLL]) with an anti-CD19 CAR T cell product, engineered to express CD28 as co-stimulatory domain. No conditioning regimen was used. As opposed to first-generation CAR T cells, persistence of the product was observed up to 6 months, with stable disease obtained in 2 patients.[13] A similar construct was used at the same time by investigators at the National Cancer Institute (NCI), first in a patient with relapsed FL, and subsequently in 15 patients

with either relapsed or refractory DLBCL, CLL or indolent lymphomas. Conditioning with fludarabine and cyclophosphamide was used, to decrease the risk of rejection of the CAR T cells. This approach resulted in prolonged product persistence and significant clinical activity with 8 complete responses [CR] and 4 partial responses [PR] in the 13 evaluable patients. However, grade 3 or greater toxicity was observed in all patients, including cytokine release syndrome (CRS) and neurotoxicity, but all resolving within 3 weeks.[14,15] Of interest, in a subsequent trial conducted by the same group, the use of a less intense conditioning therapy resulted in a significantly lower rate of severe toxicity (55%), despite comparable product persistence and clinical activity.[16]

Multicenter axi-cel trial and FDA approval. The encouraging results observed with axicabtagene ciloleucel or axi-cel (the 2nd generation CAR developed at the NCI) led to its evaluation further in a multicenter single-arm phase II clinical trial in relapsed or refractory aggressive B-cell lymphomas, the ZUMA-1 study. Seven patients with relapsed or refractory DLBCL were enrolled in the phase I component of the ZUMA-1 trial, and conditioning consisted of both cyclophosphamide and fludarabine.[17] In the subsequent phase II component of the study, 101 patients with relapsed or refractory DLBCL, t-FL and primary mediastinal B-cell lymphoma (PMBCL) were treated using the same conditioning regimen. In the combined phase I plus phase II study of 108 patients, ORR was 83%, CR rate 58%, and grade 3 or higher cytokine release syndrome (CRS) and immune-cell associated neurotoxicity syndrome (ICANS) were reported in 11% and 32% of patients, respectively.[18,19] These results led to FDA approval of this product, marketed as Yescarta, in October 2017 for patients with relapsed or refractory DLBCL, PMBCL, t-FL, and high-grade B-cell lymphoma after at least 2 lines of systemic therapy. Recently, the long term activity of axi-cel has been reported: at a median follow-up of 27.1 months, the median progression-free survival was 5.9 months, median overall survival has not been reached, and 39% of the patients were in ongoing remission.[19] Improved therapeutic and preventive treatments require a better understanding of CRS and ICANS physiopathology, which has so far remained elusive.

4.1.2 Physiopathology of CRS and ICANS

Cytokine release syndrome (CRS). CRS results from rapid activation and proliferation of CAR T cells, with subsequent supraphysiologic release of pro-inflammatory cytokines from the CAR T cells themselves as well as bystander immune cells.[20] It can manifest with fever, hypotension, hypoxia, and signs/symptoms of organ dysfunction. CRS typically peaks at time of maximal in vivo CAR T cell expansion, and resolves within 3 weeks from the infusion.[21,22] Most patients experience grade 1-2 CRS, however, severe toxicity may occur in patients with bulky disease. Severe CRS has been associated with serum IL-6 levels and tocilizumab, an anti-IL-6 receptor antibody, has been used successfully for CRS management. Severe CRS, refractory to tocilizumab, may require use of corticosteroids, which can suppress multiple immune cells and downregulate production of multiple cytokines.[23] Rarely, patients may develop fulminant macrophage activating syndrome or hemophagocytic lymphohistiocytosis following CAR T therapy.[18,23] Such patients are also initially managed with anti-IL6 and corticosteroid therapy, before considering other therapies such as etoposide.[24]

Immune cell-associated neurotoxicity syndrome (ICANS). The pathophysiology of neurotoxicity, also referred to as CAR-related encephalopathy syndrome (CRES) or immune effector cell-associated neurotoxicity syndrome (ICANS), remains largely unknown.[20,23] Possible mechanisms include diffusion of cytokines and transmigration of CAR T cells into the central nervous system, activation of endothelial cells and disruption of the blood-brain barrier, and activations of myeloid cells by IL-1, GM-CSF, and possibly other cytokines.[25-30] It typically presents as toxic encephalopathy, with word-finding difficulty, aphasia, altered level of consciousness, and impairment of cognitive skills, and in more severe cases, motor weakness, seizures, and cerebral edema. Like CRS, most patients experience grade 1-2 neurotoxicity and it is usually self-limiting and completely reversible. Neurotoxicity occurring concurrently with CRS can be successfully treated with CRS-directed therapy. However, severe neurotoxicity occurring in the absence of CRS may require use of corticosteroids and intensive monitoring and supportive care through a multidisciplinary team.[23]

4.1.3 Preclinical and Clinical Trial Data with Anakinra

Role of IL-1 in CRS and ICANS. To study CRS in the absence of GVHD, Norelli et al used human T cells that had matured in humanized mice and hence were tolerant to mouse antigens (xenotolerant).[28] When infused into humanized mice, CD19- and CD44v6-modified CAR-Ts expanded in response to human CD19+ B cells and CD44v6+ monocytes eliminated these normal cells and induced severe CRS-like toxicity that was enhanced in the presence of tumor. As greater monocyte numbers in humanized mice were associated with more severe CRS, the authors investigated the role of monocytes in CRS. Monocyte depletion in tumor-bearing, humanized mice before CAR-T infusion completely eliminated CRS without preventing leukemic remission. However, tumor elimination was delayed, and CAR-T expansion was reduced. Further, CD44v6 CAR-Ts used to eliminate human monocytes in mice before leukemia engraftment responded poorly to leukemic cells, and tumor responses were reduced. These results suggest that myeloid cells may be important for CAR-T efficacy in addition to having a role in CRS. In addition, to study the role of cytokines in the induction of CRS, Norelli et al evaluated the kinetics of cytokine production by monocytes in co-cultures with CD19.CAR T cells and leukemic cells. IL-1 preceded IL-6 by 24 h. Giavridis et al produced a CRS-like syndrome in immunodeficient beige mice after infusion of CD19.28z CAR-Ts, but only if the CAR-Ts were infused intraperitoneally and only in mice with a high tumor burden.[29] Notably, CRS was not induced in more immunodeficient NSG mice using the same conditions, likely because unlike beige mice, NSG mice harbor defects in (IL-6- and IL-1-producing) monocytes and macrophages. CRS in beige mice was accompanied by an increase in both human and mouse cytokines and chemokines and by massive infiltration of mouse myeloid cells, mostly macrophages, into the tumor site and the spleen. Intratumoral murine macrophages were the major source of lL-6, and a murine IL-6-receptor antibody infused at the time of CAR T cell infusion prevented CRS-induced mortality, showing that human CAR-Ts are able to activate murine macrophages. CRS was enhanced by expression of murine CD40 ligand on the human CAR-Ts, highlighting the importance of cell-to-cell contact between macrophages and CAR-Ts. This interaction induced inducible nitric oxide synthase (iNOS) from tumor-infiltrating macrophages.

Pre-clinical activity of anakinra for CRS and ICANS. In their mouse model, Norelli et al

blocked the receptor for both IL-1 (with anakinra) and IL-6 at the time of CAR-T infusion prevented CRS without affecting CAR-T expansion or leukemic clearance.[28] Unexpectedly, about 30 days post-infusion, mice that had received prophylactic IL-6-receptor blockade developed lethal neurotoxicity. Importantly, mice that received prophylactic anakinra remained free of neurotoxicity, and only anakinra could prevent both CRS and neurotoxicity. In the mouse model developed by Giavridis et al, severe CRS toxicity could also be alleviated by iNOS inhibitors.[29] As iNOS is induced by both IL-1 and IL-6, the authors also blocked IL-1 receptor signaling with Anakinra, which, as in the study of Norelli et al, prevented CRS. The authors went on to show that CAR-Ts expressing a recombinant IL-1-receptor antagonist could also inhibit CRS without loss of tumor control. This CAR-T intrinsic strategy could eliminate the requirement for administration of expensive recombinant proteins after CAR-T infusion.

Current clinical use of anakinra. Anakinra is currently approved for the treatment of patients with rheumatoid arthritis (RA) who have failed 1 or more lines of disease modifying anti-rheumatic drugs, and for the treatment of patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), a form of Cryopyrin-Associated Periodic Syndromes (CAPS).[31-34] Anakinra is used at the dose of 100 mg subcutaneously daily in RA, and 1-2 mg/Kg (up to 8 mg/Kg) subcutaneously daily for patients with NOMID/CAPS. Every other day dosing is recommended in case of creatinine clearance < 30 mL/min. In patients with RA, the most common adverse reactions (incidence ≥ 5%) are injection site reaction, worsening of RA, upper respiratory tract infection, headache, nausea, diarrhea, sinusitis, arthralgia, flu like-symptoms, and abdominal pain; in patients with NOMID/CAPS, the most common AEs during the first 6 months of treatment (incidence >10%) are injection site reaction, headache, vomiting, arthralgia, pyrexia, and nasopharyngitis. For study details please refer to the Investigator's Brochure.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As described above, IL-1 blockade can associate with reduction of CRS and ICANS, without affecting axi-cel efficacy. Therefore, administration of anakinra without affecting efficacy may increase the safety and potentially the efficacy of axi-cel in patients with relapsed or refractory large B-cell lymphoma. Based on the known mechanisms of action of anakinra and axi-cel and their established safety profile, the combination is not expected to increase the toxicity of either agent. No other clinical trials are currently investigating this combination, this being a pilot study. Given that the many patients with relapsed or refractory B-cell lymphoma in need of CAR T cell therapy are older or with significant comorbidities, development of such therapeutic strategies that without affecting efficacy increase safety and potentially the efficacy of axi-cel is highly desirable.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The absolute bioavailability of anakinra after a 70 mg subcutaneous bolus injection was evaluated in 11 healthy subjects and was 95%. In 18 subjects with RA, maximum plasma concentrations occurred 3 to 7 hours after administration at clinically relevant doses (1 to 2

mg/kg): the terminal half-life ranged from 4 to 6 hours and no unexpected accumulation of was observed after daily subcutaneous doses for up to 24 weeks.[35]

The safety and efficacy of anakinra have been evaluated in 3 randomized, double-blind, placebo-controlled trials of 1392 patients ≥ 18 years of age with active RA. An additional fourth study was conducted to assess safety.[35] In the efficacy trials, anakinra was studied in combination with other disease-modifying antirheumatic drugs (studies 1 and 2) or as a monotherapy (study 3). The highest investigated dose was 100 mg daily. The most serious adverse reactions were neutropenia (any grade, 8% of patients) and infections (grade 3-4 in 2% of patients), and more common in patients receiving other immunosuppressive agents.

The safety and efficacy of anakinra have also been investigated in an open label study including 43 patients with NOMID/CAPS, using doses up to 8 mg/Kg daily, for up to 15 months.[35] The most serious adverse reaction was represented by infections, reported in 7 patients (grade 3-4), and more common in patients < 12 years.

The dose of anakinra typically used for the treatment of RA (100 mg daily) may or may not be biologically effective for the purpose of IL-1 blockade in patients with relapsed or refractory large B-cell lymphoma receiving axi-cel therapy. The 2 dose levels selected for this study (100 mg daily and 100 mg BID), corresponding to a dose ranging between 1 mg/Kg and 6 mg/Kg, are based on safety established in clinical trials with doses as high as 8 mg/Kg, used for prolonged time. In addition, as the dosage form is a pre-filled syringe of 100 mg for subcutaneous use, selected dose levels will limit the treatment to no more than 2 subcutaneous injection a day for treated patients. The duration of treatment of 7 days, starting on day 0 of axi-cel infusion, is based on the kinetics of IL-1RA observed in patients with large B-cell lymphoma treated with axi-cel,[36] showing the highest concentrations in the peripheral blood of treated patients during the first week after axi-cel infusion.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety and Efficacy Endpoints

The primary endpoint is the safety and tolerability of anakinra in decreasing CAR T cell-related toxicity measured as incidence of any grade CR within 30 days after infusion of CAR T cells in patients with relapsed or refractory large B-cell lymphoma. Secondary efficacy endpoints will include incidence of different grades and duration of both CRS and ICANS, ORR, CR rate, PFS, and OS. Cheson 2014 Lugano Classification response criteria for malignant lymphoma will be used to assess clinical responses.[1] After prolonged follow-up, use of axi-cel in patients with relapsed or refractory large B-cell lymphoma was associated with an ORR of 83%, a CR rate of 58%, and a rate of grade 3 or higher CRS and ICANS of 11% and 32%, respectively.[18,19] Given the mechanism of action of anakinra and the absence of significant overlapping toxicity, we expect to observe a reduction in CRS and ICANS, without any additional AEs. We may also observe an improvement in ORR, CR rate, PFS and OS as compared with axi-cel monotherapy.

4.2.3.2 Biomarker Research

Blood samples and tumor biopsies will be obtained from consenting patients at baseline and/or on treatment from subjects enrolled on the study at the indicated time points shown in the Trial Flow Chart under Section 6.0. The overall goal of the biomarker studies is to identify pharmacodynamic effects of anakinra combined with axi-cel therapy. Peripheral blood mononuclear cells (PBMC) and plasma will be isolated from blood samples and cryopreserved for batched analysis. Both blood sample and tumor biopsy collection are optional.

PBMC samples will be analyzed by up to 14-color multiparametric flow cytometry to determine the expansion, phenotype, and persistence of CAR T cells as well as alteration in the phenotype and number of multiple cellular components, including normal B and T lymphocytes, monocytes, and natural killer cells. Plasma samples will be analyzed for alteration in various cytokines and chemokines. CAR T cell levels will also be monitored by qPCR.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male or female subjects with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, transformed follicular lymphoma or high-grade B-cell lymphoma receiving standard of care therapy with axicabtagene ciloleucel.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Relapsed or refractory DLBCL, PMBCL, tFL, or HGBCL, at least 2 prior lines of systemic therapy
2. Planned to receive standard of care therapy with axicabtagene ciloleucel
3. ≥ 18 years of age
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Appendix 1**)
5. Measurable disease of ≥ 1.5 cm
6. At least two weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for axi-cel therapy, except for systemic immune checkpoint inhibitory / immune stimulatory therapy. At least 3 half-lives must have elapsed from any prior systemic immune checkpoint inhibitory / immune stimulatory therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc)
7. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)

8. Absolute neutrophil count of ≥ 1.0×10^9/L
9. Platelet count of ≥ 60×10^9/L
10. Creatinine clearance (as estimated by Cockcroft Gault) ≥ 45 mL/min
11. Serum alanine transaminase (ALT) / aspartate transaminase (AST) ≤ 2.5 upper limit of normal (ULN)
12. Total bilirubin ≤1.5 mg/dL, except in subjects with Gilbert's syndrome.
13. Cardiac ejection fraction ≥ 50% with no evidence of pericardial effusion
14. Baseline oxygen saturation > 92% on room air
15. No evidence, suspicion, and/or history of lymphoma involving the central nervous system (CNS)
16. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) unless disease free for at least 3 years
2. History of Richter's transformation of chronic lymphocytic leukemia (CLL)
3. Autologous stem cell transplantation within 6 weeks of planned axi-cel infusion
4. History of allogeneic stem cell transplantation
5. Prior CD19 targeted therapy
6. Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
7. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Principal investigator
8. Known history of infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
9. Known history of tuberculosis. A negative Quantiferon or PPD up to 2 months before start of anakinra is enough if no specific risk factors
10. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted

11. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases
12. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
13. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
14. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment
15. Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
16. Primary immunodeficiency
17. History of autoimmune disease (e.g. Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years
18. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment
19. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
20. History of severe immediate hypersensitivity reaction to any of the agents used in this study, including E coli-derived proteins
21. Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen
22. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.
23. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of anakinra injections
24. In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participationTrial Treatments

5.1.4 Dose Selection/Modification

5.1.4.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. The 2 dose levels of Anakinra to be used in this trial are outlined below in **Table 1**. A 3+3 design will be used for a safety run-in phase within each dose level cohort.

Table 1. Dose levels (DL)

Drug	Potency	Frequency	Route of Administration	Treatment Period
DL1: Anakinra	100 mg	daily	subcutaneous	7 days, starting on day 0 of axi-cel infusion
DL2: Anakinra	100 mg	Twice a day	subcutaneous	7 days, starting on day 0 of axi-cel infusion

5.1.4.2 Guidelines for Dose Modification

Dose modifications of anakinra are not permitted within each subject. Any subject who experiences toxicity from anakinra may be discontinued from further injections of anakinra at the discretion of the Principal Investigator.

5.1.5 Timing of Dose Administration

Administration of conditioning chemotherapy. Subjects will receive cyclophosphamide (500 mg/m2/day) and fludarabine (30 mg/m2/day) for 3 days on days -5, -4, and -3. Weight of the subject measured at any time between days -14 and -5 may be used for calculation of chemotherapy doses. Antiemetic prophylaxis, mesna, and intravenous hydration will be included as per standard guidelines. The administration start/stop time of cyclophosphamide, fludarabine, and mesna will all be noted in the subject medical record.

Administration of axi-cel. Subjects will be hospitalized for axi-cel infusion. Axi-cel treatment consists of a single infusion of CAR transduced autologous T cells administered on day 0 in under 30 minutes. Axi-cel will be infused intravenously via a central venous catheter at a dose of 2×10^6 anti-CD19 CAR^+ T cells/kg with a maximum of 2×10^8 CAR^+ T cells for patients weighing >100 kg. Body weight on the day of leukapheresis will be used for calculation of axi-cel dose. Subjects will remain in the hospital through at least day 7 post-axi-cel infusion. Subjects should not be discharged from the hospital until all axi-cel-related non-hematological toxicities return to ≤ grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (e.g., renal insufficiency) even if > grade 1, if deemed appropriate by the Principal Investigator.

Administration of anakinra. The study drug, anakinra will be administered daily by subcutaneous injection for 7 days. The initial dose will be administered on day 0, at least 6 hours prior to axi-cel infusion. Two dose levels will be investigated: 100 mg daily and 100 mg BID. A 3+3 design will be used for a safety run-in phase within each dose level cohort.

5.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator and the subject.

5.2.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Subjects may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 7.2.

5.2.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than anakinra
- Radiation therapy
- Live vaccines within 6 weeks prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic use of glucocorticoids for any purpose other than for management of CAR-T associated toxicities during the first 30 days after axi-cel infusion. The use of physiologic doses of corticosteroids may be allowed (</= 5 mg/day of prednisone or equivalent doses of other corticosteroids).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.3 Rescue Medications & Supportive Care

5.3.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Infection Prophylaxis: Subjects should receive prophylaxis for pneumocystis pneumonia, herpes simplex/zoster, and fungal infections according to standard institutional practice.
- Tumor Lysis Syndrome: all subjects with significant malignancy burden and without a contradiction such as allergy should be started on prophylaxis (e.g. allopurinol) as per institutional guidelines prior to axi-cel infusion. Prophylaxis may be discontinued when the risk of tumor lysis has passed.
- B Cell Depletion: it is possible that B cell depletion and hypogammaglobulinemia will occur due to the effects of axi-cel on normal B cells. Gammaglobulin will be administered for hypogammaglobulinemia according to institutional guidelines.
- Fever and Neutropenia: evaluation for source of infection, antipyretics, initiation of antibiotics, and comfort measures including IV hydration should be performed per institutional guidelines.
- Blood Product Support: all blood products should be irradiated. Subjects should receive platelets and packed red blood cells as needed. Attempts should be made to keep hemoglobin >8.0 gm/dL and platelets >10,000/mm3. Leukocyte filters should be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBC's and decrease the risk of CMV infection.

5.3.1.1 Supportive Care Guidelines for CRS and ICANS

Acute toxicities associated with axi-cel infusion include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Efforts should be made to rule out neoplastic, infectious, metabolic, or other causes prior to labeling an AE as CRS or ICANS.

Cytokine release syndrome (CRS). CRS is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes. The condition results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area and subject's immune cells activated during this process. When cytokines are released, a variety of clinical signs and symptoms associated with CRS present themselves including cardiac, gastrointestinal, laboratory (coagulation, renal and hepatic), neurological, respiratory, skin, vascular (hypotension) and constitutional (fever, rigors, headaches malaise, fatigue arthralgia, nausea and vomiting).

The goal of CRS management after CAR T cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects. The ASTCT (American Society for Transplantation and Cellular Therapy) CRS Consensus Grading system will be used to assess the severity of CRS (**Appendix 2**; Lee et al 2018) as well as guide management. However, we will also capture the individual data elements to be able to assess the CRS according to the grading described by Lee et al 2014 (**Appendix 3**) in order to compare the toxicities to historical data. The diagnostic work-up and management of CRS will be performed as per CARTOX Guidelines (**Appendix 5**).

Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS). CRS and classic acquired HLH/MAS have many shared features, and the 2 entities likely are not distinct, reflecting the activation of the reticuloendothelial system initiated by T cell-mediated inflammation. Most patients with moderate to severe CRS have laboratory

results that meet the classic criteria for HLH/MAS such as elevation of ferritin, triglycerides, and soluble CD25 but may or may not have hepatosplenomegaly, lymphadenopathy, or overt evidence of hemophagocytosis. The symptoms and signs suggestive of HLH/MAS subside with CRS resolution in most patients. However, refractory and fulminant HLH/MAS has been described in rare cases after CAR T-cell therapy and may be treated as previously described using tocilizumab and corticosteroids with or without etoposide.[23]

Immune effector cell-associated neurotoxicity syndrome (ICANS). Neurotoxicity (e.g. encephalopathy, somnolence, aphasia) have been observed with anti-CD19 CAR T cell therapies. The ASTCT Consensus Grading will be used for to assess the severity of ICANS (**Appendix 4**; Lee et al 2018) as well as guide the management. However, we will also grade and capture the symptoms and signs of neurotoxicity as per CTCAE v 5.0 in order to be able to compare the toxicities to historical data. The diagnostic work-up and management of ICANS will be performed as per CARTOX Guidelines (**Appendix 6**).

Endotracheal intubation may be needed for airway protection in severe cases. Corticosteroids may be considered for any severe or life-threatening neurotoxicity and anti-seizure and sedatives may be considered as clinically indicated. If there is no contraindication, subjects will receive levetiracetam (750 mg PO or IV BID) for seizure prophylaxis starting on Day 0. Levetiracetam may be tapered and discontinued after day 30.

5.4 Other Considerations

5.4.1 Contraception

Chemotherapy agents used for conditioning before axi-cel infusion and anakinra may have adverse effects on a fetus in utero. Furthermore, it is not known if anakinra has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study visit 1 and throughout the study period up to 6 months after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Sobi. If there is any question that a subject

will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.4.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with anakinra, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Sobi without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Sobi. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Sobi and followed as described above and in Section 7.2.2.

5.4.3 Use in Nursing Women

It is unknown whether anakinra is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable AEs (grade $\geq$ 3 AE lasting > 2 weeks)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

5.6 Subject Replacement Strategy

Additional subjects may be enrolled to ensure that the required number of evaluable subjects is achieved in the applicable analysis population.

5.7 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies with anakinra indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug
5. Evidence of significant Dose-limiting toxicity (DLT) at dose level 1 as defined in Section 8.1.

In the event of Sobi decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Schedule of Assessments – Table 2.

Procedures	**Screening (Days before enrollment)**	**Enrollment**	**Conditioning Chemotherapy Period**					**CAR-T cell Administration Period**		**Post Treatment Follow-up (each visit calculated from Day 0)**			
Day	Within 28 days of enrollment		-5	-4	-3	-2	-1	0	1 - 7	Week 2	Week 4 (± 3 days)	Month 2 (± 1 week)	Months 3, 6, 9, 12, 18, 24 (± 2 weeks)
Medical history	X												
Physical exam[k]								X	Daily	X	X	X	X
Neurological assessment[k]								X	Daily		X		X (month 3)
ECOG Performance Status[k]													
ECG	X												
LVEF assessment by ECHO[a]	X												
Leukapheresis	X												
Fludarabine/Cyclophosphamide			X	X	X								
Axi-cel infusion IV								X					
Anakinra[i]								X	Daily (days 1-6)				
Brain MRI	X												
PET-CT/ CT CAP for disease	X[b]										X		X
ICE Score[k]								X	X	X	X		
Vital signs[c]	X		X	X	X			X	Daily	X	X	X	X
Weight and height[d]	X		X	X	X			X					
Pregnancy test (serum or urine)[e]	X		X										
Urinalysis	X												
Chemistry panel	X		X					X	Daily	X	X	X	X
CBC w/differential	X		X					X	Daily	X	X	X	X
PT, PTT	X		X					X	Weekly	X	X	X	X
CRP and ferritin levels			X					X	Daily				

IgG, IgM, IgA			X								X		X
HIV and Hepatitis serology	X[f]												
ELISpot for tuberculosis	X												
Bone marrow biopsy/aspirate	X[j]										X[g]		X[g]
Blood draw for biomarkers			X					X	Days 1, 3, 7	X	X		X
Adverse events/ Concomitant medication	X		X	X	X	X	X	X	X	X	X[h]		

[a]ECHO is acceptable if it is performed within 6 weeks of enrollment.
[b]PET-CT (Neck-Chest-Abdomen-Pelvis)/disease assessment PET-CT performed following last line of therapy (>28 days from enrollment) may be used for confirmation of eligibility. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. As applicable, bone marrow aspirate/biopsy will be performed to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42 days prior to the first dose of trial treatment
[c]Vital signs should include temperature, pulse, respiratory rate blood pressure and oxygen saturation
[d]Weight will be measured at any time between days -14 and -5may be used for calculation of chemotherapy doses. Body weight will be collected on the day of leukaphersis. Height will be measured at screening only.
[e] For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
[f]Test for HIV, hepatitis B and C serology to be performed within 60 days of enrollment; PCR will be performed only in case of positive serology, for confirmation
[g]This will be repeated at time of first response assessment if initially positive and patient has achieved CR by PET-CT
[h]If possible, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.
[i] The initial dose will be administered on Day 0 approximately 6 hours prior to Axi-cel infusion
[j] Screening bone marrow biopsy and aspirate can be waived if PET-CT and/or blood counts, at the discretion of the treating physician, are not concerning for lymphoma involvement
[k] Within 28 days of starting treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If possible, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or a physician designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. CRS and ICANS will be graded according to the ASTCT consensus guidelines and Lee et al 2014. Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam and Vital Signs

The investigator or qualified designee will perform a full physical exam during the screening period. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs. The investigator or qualified designee will also take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure, oxygen saturation. Height will be measured at screening only.

7.1.2.3 Neurocognitive Assessment and Magnetic Resonance Imaging

Neurocognitive assessments will be standardized by using the Immune-Effector Cell-Associated Encephalopathy (ICE) Score as per ASTCT consensus grading (**Appendix 4**). A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before axi-cel administration on Day 0 and on day 1-7 as well as week 4 and month 3. If CNS symptoms develop, ICE score will be performed daily until resolution of symptoms or discharged from the hospital. Each subject will undergo a screening Brain MRI to rule out CNS metastasis during the screening period of the study.

7.1.2.4 Cardiac Function

Each subject's cardiac function as measured by Left Ventricular Ejection Fraction (LVEF) will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. To establish a baseline, a 12-lead ECG will also be performed prior to initiating study treatment.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Criteria for Assessment of Disease

The Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[1] criteria will be applied as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy) (**Appendix 7**).

7.1.2.6.2 Initial Disease Assessment

Initial disease assessment or tumor imaging must be performed within 28 days prior to the first dose of trial treatment. PET-CT fusion imaging scans with oral contrast/water and IV contrast will be used for initial disease assessment unless there is a contraindication. Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42 days prior to the first dose of trial treatment.

7.1.2.6.3 Disease Assessment During Trial

Disease response assessments will occur 4 weeks after initiation of therapy, then at months 3, 6, 9, 12, 18, and 24. There is a ±14-day window for all imaging assessments. Disease response assessments will be performed by CT scans or PET-CT scan at the indicated time points (see Trial Flow Chart - Section 6.0).

In subjects achieving a complete remission by CT scan criteria, PET-CT scan will be repeated once to confirm response. In addition, unilateral bone marrow aspiration and biopsy will be repeated once in such patients if the bone marrow was involved with lymphoma at baseline.

Disease assessments and imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

7.1.2.7 Blood Sampling and Tumor Tissue Collection for Correlative Studies

Biomarker analysis will be performed on blood and tumor samples to evaluate the effects of anakinra on mechanisms of CRS, ICANS and on the function of infused CAR T cells. Prognostic markers in large B-cell NHL may also be evaluated.

The expansion, persistence, and immunophenotype of transduced anti-CD19 CAR+ T cells will be monitored in the blood primarily by PCR analysis, complemented by flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-8, IL-1, IL-2, GM-CSF, IL 15, IL-17a, IFNγ, IL-12p40/p70; immune effector

molecules Granzyme A, B, Perforin, sFasL; correlates of acute phase response CRP, SAA and chemokines MIP-1α, MIP-3α, IP-10, Eotaxin, MCP-4.

These samples and any other components from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the central laboratory. The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the investigator and any data that may be generated will be entered in the study database.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The schedule for laboratory assessments is provided under the Trial Flow Chart.

Laboratory tests for screening or entry into the trial should be performed within 28 days prior to the first dose of treatment. Pre-dose laboratory procedures will be conducted daily prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

The schedule for laboratory assessments is provided under the Trial Flow Chart. CBC with differential should include total white count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, and platelet count. Comprehensive serum chemistry panel should include sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH). Direct bilirubin should be obtained if total bilirubin is above the upper limit of normal. Coagulation indexed will include PT and PTT. Urinalysis should include blood, glucose, protein, and specific gravity. HIV and Hepatitis serology (including PCR in case of positive serology, for confirmation). ELISpot for tuberculosis.

7.1.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation, if the patient consents. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording AEs, if the patient consents. After discontinuing treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.2) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3). However, the follow-ups do not apply when consent and/ or authorization are withdrawn by the subject.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Post-Treatment Safety Follow-Up Visit

If possible, the Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should be followed and recorded.

7.1.5.3 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed by radiologic imaging to monitor disease status. Imaging assessments will be performed every 3 months during the first year and every 6 months during the second year. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study.

7.2 Assessing and Recording AEs

Data will be recorded in RedCap. CORe database will be used along with RedCap for subject registration.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the anakinra, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, onset of menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the use of anakinra in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All AEs will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the AE CRFs/worksheets. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting. The AE reporting guidelines are detailed in Table 3 below:

Table 3: AE Reporting Guidelines

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure.

- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for anakinra by 20% over the prescribed dose. No specific information is available on the treatment of overdose of anakinra. In the event of overdose, anakinra should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of anakinra, the AE(s) is reported as a serious AE, even if no other seriousness criteria are met.

If a dose of anakinra meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a

non-serious AE, using the terminology "accidental or intentional overdose without adverse effect."

Overdoses must be reported within 2 working days to MD Anderson Cancer Center IND Office (IND Sponsor) and Swedish Orphan Biovitrum AB, unless they are life threatening or result in an SAE in which case they will be reported within 24 hours to MD Anderson Cancer Center IND Office (IND Sponsor).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Sobi

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 2 working days to MD Anderson Cancer Center IND Office (IND Sponsor) and Swedish Orphan Biovitrum AB, unless they are life threatening or result in an SAE in which case they will be reported within 24 hours to MD Anderson Cancer Center IND Office (IND Sponsor).

7.2.3 Immediate Reporting of AEs to the Sponsor and to Sobi

7.2.3.1 Serious Adverse Events (SAEs)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this

definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office and within 2 working days to Swedish Orphan Biovitrum AB.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to anakinra, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

All SAEs will be reported within 2 working days to Swedish Orphan Biovitrum AB.

A copy of all 15-Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross-reference this submission according to local regulations to Swedish Orphan Biovitrum AB at the time of submission. Additionally investigators will submit a copy of these reports to Swedish Orphan Biovitrum AB at the time of submission to FDA.

7.2.4 Evaluating AEs

Severity of the adverse events (AEs) -The severity of the adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.5.0. Events not included in the NCI CTCAE will be scored as follows:

General grading:

- **Grade 1**: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2**: Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3**: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4**: Life Threatening: discomfort that represents immediate risk of death

Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets. CRS and ICANS will be assessed according to the ASTCT consensus guidelines and Lee et al 2014. All AEs regardless of CTCAE grade must also be evaluated for seriousness.

8.0 STATISTICAL CONSIDERATIONS

This is an open label, pilot designed to evaluate the safety, tolerability and early efficacy of anakinra by subcutaneous injection for 7 days starting on day 0 of axicabtagene ciloleucel (axi-cel) treatment in patients with relapsed or refractory DLBCL, PMBCL, transformed FL, and high-grade BCL. Anakinra will be tested at a dose level of 100 mg daily and 100 mg BID. A 3+3 design will be used for a safety run-in phase within each dose level of Anakinra.

The study consists of two phases within each dose level cohort: 1) safety run-in phase, and 2) expansion phase. The maximum number of patients that will be recruited for the study is 20: for each dose level cohort, according to 3+3 design, a maximum of 6 patients will be enrolled, and 4-7 additional patients will be enrolled during the escalation phase, for a maximum of 10 patients per dose level cohort.

8.1 Part 1: Safety Run-in Phase

The objective of the safety run-in phase is to investigate the safety and tolerability of anakinra in combination with axi-cel in patients with relapsed or refractory large B-cell lymphoma.

A standard 3+3 design will be employed within each dose level cohort. Patients will be treated in cohorts of size 3 to 6 and the dosage will be claimed safe if the clinical toxicity is acceptable.

Dose-limiting toxicity (DLT) is defined as the following sequenced therapy-related events (Sequenced therapy refers to the addition of anakinra to the approved axi-cel treatment regimen.) with onset within the first 28 days following the start of anakinra and axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 28 days from the day of cell transfer
- Any sequenced therapy-related AE requiring intubation, including Grade 4 encephalopathy requiring intubation for airway protection, is considered to be a DLT
- Any sequenced therapy-related Grade 5 event
- All other clinically significant Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following conditions which are not considered DLT's:
    - Encephalopathy that resolves to at worst Grade 1 within 2 weeks and to baseline within 4 weeks
    - Grade 3 fever
    - Myelosuppression (includes bleeding in the setting of platelet count < 50 x 10^9/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia, and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above
    - Immediate hypersensitivity reactions occurring within 2 hours of cell infusion or anakinra injection that are reversible to Grade 2 or less within 24 hours of administration with standard therapy
    - Renal toxicity which requires dialysis for ≤ 7 days
    - Tumor lysis syndrome including associated manifestations attributable to tumor lysis syndrome (eg, electrolyte abnormalities, renal function, hyperuricemia
    - Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation that resolve to ≤ Grade 2 within 14 days

- Grade 4 transient serum hepatic enzyme abnormalities that resolve to ≤ Grade 3 within < 72 hours
- Grade 3 or 4 hypogammaglobulinemia
- Grade 3 nausea or anorexia

If grade 3 or 4 changes in vital signs and/or neurological status are not due to CRS or ICANS but to one of the exceptions above, the event will not be considered a DLT.

The dose can be claimed safe if at most one out of six patients treated had DLT. The design scheme is as follows:

Table 4. Decision Rules for 3+3 Design Schema

Number of Patients with DLT at a Dose Level	**Decision**
0 of 3	Claim the dose is safe and proceed to the expansion phase.
1 of 3	Enroll 3 additional subjects at this dose level.
>/=2 of 3	Claim the dose level is too toxic. An alternative dose or schedule may be explored.
1 of 6	Claim the dose is safe and proceed to the expansion phase.
>/=2 of 6	Claim the dose level is too toxic. An alternative dose or schedule may be explored.

Frequencies of toxicities will be tabulated according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5.0. CRS will be assessed by both Lee 2014 criteria as well as ASTCT Consensus Grading system. ICANS will be assessed by both CTCAE v5.0 as well as ASTCT Consensus Grading system. Patients will be continued to be followed for one year for evidence of late toxicity.

Data from all subjects who receive the study drug will be included in the safety analyses. Subjects who entered the study and did not take the study drug and had this confirmed, will not be evaluated for safety. Safety and efficacy data will be reviewed after each 3-6 patient cohort will complete 30 days of treatment during the safety run-in phase, and accrual will be placed on hold while this analysis is pending. If there is unacceptable study drug-related toxicity, the study will be placed on hold and no further treatment of any patient will occur until further review and discussion with the FDA. The study may proceed after appropriate amendments have been made to address the observed study drug-related toxicity.

8.2 Part 2: Expansion phase

Additional 4-7 patients will be treated, for a total of 10 patients per dose level cohort, to further investigate safety and tolerability of the combination and in order to explore preliminary evidence of efficacy. Once each dose level cohort is completed, a Safety

Review Team (SRT), consisting of the PI, Co-PI, and Biostatistician, will review the data and make recommendations based on overall safety profile of the combined treatment regimen. Rate and grade of CRS and ICANS during the first 30 days after the first injection of anakinra will be considered efficacy endpoints. Quality of response to axi-cel, as determined by Lugano criteria, and progression-free survival will also be considered an efficacy endpoint.

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety.

Safety and efficacy data will be reviewed after 3-6, and 10 patients have completed 30 days of treatment for each dose level, and accrual will be placed on hold while this analysis is pending. If there is unacceptable study drug-related toxicity, the study will be placed on hold and no further treatment of any patient will occur until further review and discussion with the FDA. The study may proceed after appropriate amendments have been made to address the observed study drug-related toxicity.

The Investigator is responsible for completing safety/efficacy summary reports and submitting them to the IND Office Medical Affairs and Safety Group for review and approval. These should be submitted as follows:

- Run-In Phase:

After the first 3 evaluable patients per dose level, complete 30 days post CAR-T cell infusion, and after the first 6 evaluable patients per dose level, complete 30 days post CAR-T cell infusion. IND Office approval must be obtained before advancing/changing dose levels.

- Expansion Phase

After a total of 10 evaluable subjects per dose level, complete 30 days of study treatment.

A copy of the safety summary report should be placed in the Investigator's Regulatory Binder under "Sponsor correspondence".

8.3 Power and population size calculation for efficacy endpoint

In this pilot study, 10 patients will be enrolled and treated at the lower dose level of anakinra (100 mg daily). Assuming a ICANS rate of 70% at 30 days without the treatment of anakinra,[18,37] a sample size of 10 will ensure the study with 84% power to detect the reduction to 30% in ICANS rate for the patients treated with anakinra with a one-sided type I error rate of 0.05 using an exact binomial test (nQuery Advisor 7.0). We will estimate the ICANS rate after the evaluation of the 10th patient at 30 days. If deemed safe during the safety run-in phase, we will enroll and treat a maximum of 10 patients at the higher dose level (100 mg BID). If we achieve ICANS rate of 30% or lower) with at least one of the 2 dose levels, the one producing the highest reduction will be selected for future randomized

studies. Otherwise, we will reevaluate whether a higher dose level needs to be investigated for anakinra. Even if a 30% ICANS rate is observed with the lower dose level, if deemed safe, the higher dose level will also be tested to explore the possibility to further reduce ICANS without any increase in toxicity. When the true ICANS rate is 70% for both doses, the probability of observing ICANS rate of 30% or lower for at least one dose is 0.021.When the true ICANS rate is 30% for both doses, the probability of observing ICANS rate of 30% or lower for at least one dose is 0.877. If a 30% or lower ICANS incidence rate is observed during the pilot portion by one of the anakinra doses, the study will be amended to include a subsequent portion, where the efficacy of anakinra will be compared to placebo in mitigating CAR-T toxicity in a randomized setting. If none of the anakinra doses produces a 30% or lower ICANS incidence rate during the pilot portion, then we will reevaluate whether a higher dose level needs to be investigated for anakinra.

8.4 Analysis plan

Patient demographic information, clinical characteristics, and outcomes will be summarized. CAR T cell levels in the blood, serum cytokine and chemokine levels will be reported. ICANS rate, CRS rate, response rate, and their exact 95% confidence intervals (CIs) will be estimated. Logistic regression may be utilized to assess the effect of patient prognostic factors on the response rate, the ICANS rate, and CRS rate. The distribution of time-to-event endpoints including progression free survival (PFS) and overall survival (OS) will be estimated using the method of Kaplan and Meier. Time for PFS is the time interval from the start of treatment to disease progression or death due to any cause whichever happened first. Patients would be censored at the last follow-up date if neither progression nor death occurred. Time for OS is the time interval from the start of treatment to death due to any cause. Patients would be censored at the last follow-up date if death did not occur. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies of anakinra will be provided by Sobi as summarized in **Table 6**. Rituximab will be obtained through standard commercial sources.

Table 6. Investigational Product Descriptions

Product Name & Potency	Dosage Form
Anakinra 100 mg/0.67 mL	Solution Prefilled Syringe, Subcutaneous

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication will be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Sobi or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed with MD Anderson Cancer Center IND Office (IND Sponsor), who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Sobi as a supporter of this study.

10.2 IND Safety Reports

Sobi shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Sobi and the IRB on file.

10.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.4 Data Security/Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

Access to Study Records

Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Methods of Storage of Study Records

All data collected from MD Anderson Cancer Center (MDACC) sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project

responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient-investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared.

Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors.

Duration of Study Record Storage

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Sharing of Study Records

There are no plans to share study data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

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12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Appendix3: CRS Grading as per Lee et al 2014

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose[2] of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Grades 2-4 refer to CTCAE v4.0 grading.

Definition of high-dose vasopressors

Pressor	Dose
Norepinephrine monotherapy	≥20 μg/kg/min
Dopamine monotherapy	≥10 μg/kg/min
Phenylephrine monotherapy	≥200 μg/kg/min
Epinephrine monotherapy	≥10 μg/kg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 μg/kg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 μg/kg/min*

*VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (μg/min)] + [dopamine (μg/kg/min) ÷ 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) ÷10].

Appendix 4: ASTCT Consensus Grading for ICANS

ICE Score

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Appendix 5: Management of CRS

ASTCT CRS Grade	Management
Grade 1	• Anti-pyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Consider monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen Tocilizumab + dexamethasone 10-20 mg IV q 6hrs or its equivalent of methylprednisolone
Grade 4	• Supportive care as in grade 1 • Monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/day

Appendix 6: Management of ICANS

ASTCT ICANS Grade	Management
Grade 1	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • Electroencephalogram (EEG) • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Dexamethasone 10-20 mg IV q 6hrs or its equivalent of methylprednisolone • Control any seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • For focal cerebral edema, high-dose methylprednisolone 1000 mg/day
Grade 4	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • For motor weakness, imaging of spine • For diffuse cerebral edema, lower intracranial pressure by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt

Appendix 7: Response Evaluation Criteria

Response will be determined by the Principal Investigator according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[1] and documented in the CRFs. The response criteria are summarized below:

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.